FINAL TECHNICAL REPORT

Grant No. D15AP00024
"Engineering Therapies that Evolve to Autonomously Control Epidemics"

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1. A comparison of actual accomplishments with the goals and objectives established for the grant, the findings of the investigator, or both.

The overarching aim of our seedling effort was to de-risk the idea that viruses could be engineered into therapeutics, known as Therapeutic Interfering Particles ('TIPs'), using the virus HIV as a model system. By engineering TIP prototypes that were shown to reduce HIV levels >10X in cell-culture—while having no effect on the viability of healthy, uninfected cells—we directly achieved this aim (Aim I of our proposal). The secondary aim (Aim II) of the proposal was to demonstrate, via mathematical modeling, that engineered TIPs could have indefinite, population-scale impact. To achieve this aim, we developed novel multi-scale models that connected the measured within-cell TIP dynamics achieved in Aim I with the predicted population-scale impact of these TIP prototypes on HIV prevalence levels. We further calculated cellular design constraints (e.g., genomic RNA expression levels) to guide the development of TIPs with predicted population-scale efficacy. Finally, we demonstrated the evolutionary robustness of TIPs against a key route of HIV mutational escape. Our modeling results de-risking the TIP approach were published in PLoS Computational Biology this past year.

2. Reasons why established goals were not met, if appropriate.

N/A as all established goals and metrics of success were achieved.

3. Other pertinent information.

Our seedling successes in (experimentally and computationally) demonstrating the feasibility of the TIP therapeutic concept have led to the now community-wide DARPA Intercept Program. We will be continuing to develop, test and transition TIPs as part of that program.